Journal of Critical Reviews

ISSN- 2394-5125 Vol 4, Issue 2, 2017

Review Article

GASTRORETENTIVE DRUG DELIVERY SYSTEMS: FROM CONCEPTION TO COMMERCIAL SUCCESS

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Received: 21 Dec 2016 Revised and Accepted: 04 Mar 2017

ABSTRACT

Despite the extensive advancements in the field of drug delivery, the oral route remains the favorable route for administration of therapeutic actives. A success of oral controlled drug delivery systems is associated with reduced dosing frequency, decreased fluctuation in plasma drug concentration profile along with improved patient compliance. However, they are also associated with challenges like shorter gastric residence time, unpredictable gastric emptying and poor bioavailability for some molecules. This has initiated tremendous advancements in the field of gastro-retention to achieve controlled release of drugs along with improved bioavailability of drugs with narrow absorption window as well as localized action in the stomach and upper part of GIT. In present review, efforts have been envisaged to summarize our current understanding in the field of gastro-retention and their *in vitro* as well as *in vivo* characterization. Present review also highlights commercially utilized gastro-retentive technologies and some recently granted US patents in the field of GRDDS.

Keywords: Gastro retentive drug delivery systems (GRDDS), Gastric emptying, Polymers, Bioavailability, Superporous hydrogels, Swellable matrix, Microballoons, Patents

DOI: http://dx.doi.org/10.22159/jcr.2017v4i2.16717

INTRODUCTION

In controlled drug delivery, a given drug needs to be entrapped in a platform, device or any matrix that can later on be released in a controlled way. If the drug is intended to be released at a specific site or organ and taken orally, the whole system is called oral targeted drug delivery system. One of the targets in oral controlled delivery is the stomach area. The stomach can be either a target organ or can serve as a reservoir to release the drug at the specific site. In either case, the drug is required to stay in the stomach area and the challenge will be to find ways to do the task [1].

Main challenges in designing Gastro-retentive dosage forms are shorter gastric residence time and unpredictable gastric emptying times. So before designing any GRDDS, basic understanding regarding anatomy and physiology of GIT is required to modulate gastro-intestinal transit time of drug for better absorption of drugs and site-specific drug delivery [2].

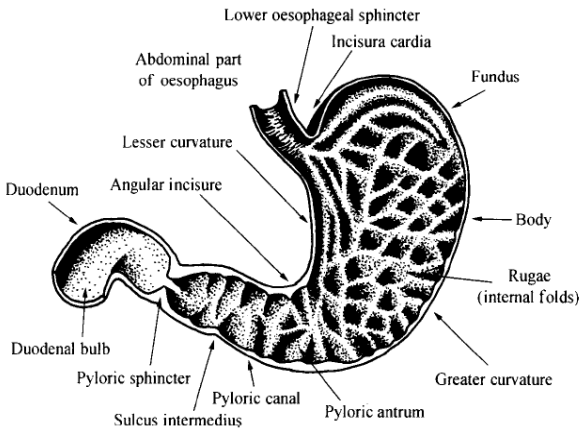

Fig. 1: Structure of the stomach (Adapted from [3])

Basic anatomy and physiological aspects of the GIT

The stomach is anatomically divided into three parts: fundus, body and pylorus (pyloric antrum and pyloric sphincter). The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region, pylorus, is the major site for mixing motions, acting as drain pump to the duodenum to accomplish gastric emptying, given in fig.1.

The complex anatomy and physiology of the GIT, including variations in acidity, bile salts, enzyme content, and the mucosal absorptive surface, significantly influence the release, dissolution, and absorption of orally administered dosage forms.

Two distinct patterns of gastrointestinal (GI) motility and secretion exist, corresponding to the fasted and fed states. As a result, the BA of orally administered drugs will vary depending on the state of feeding. The fasted state is associated with various cyclic events which cycle both through the stomach and small intestine every 2-3 h [4], commonly referred to as the interdigestive myoelectric cycle or interdigestive migration myoelectric complex (IMMC), which regulates GI motility patterns. The IMMC is organized into alternating cycles of activity and quiescence and can be subdivided into different phases[5,6], as depicted in fig. 2.

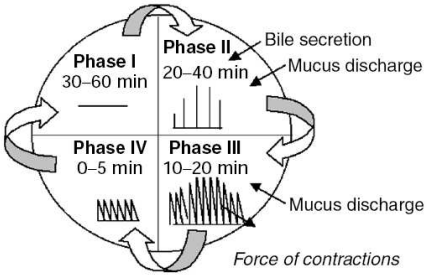

Fig. 2: Motility patterns of the GIT in the fasted state (adapted from [5])

The performance of peroral Controlled release drug delivery systems (CRDDS) is also influenced by a phase during which dosage form has been administered.

Approaches for gastric retention

Fig. 3 illustrates various approaches for gastric retention: Various approaches are available to prolong the retention of dosage forms in the stomach. The most common approaches used to increase the gastric residence time of dosage forms include high density systems, floating systems (Effervescent and non-effervesent systems), bioadhesive systems, raft forming systems, low density systems, swelling and expandable systems etc.

High density systems

Dosage forms having density from 1.0 to certain higher values can increase the average GI transit time [7]. Systems having density of ~3.0 g/cm^{3}are retained in the rugae of stomach and able to withstand its peristaltic movements. However, such type of dosage forms are technically difficult to manufacture with a large amount of drug and to achieve density of 2.4-2.8 g/cm^3. Diluents such as barium sulphate, zinc oxide, titanium dioxide can be used to prepare such high density dosage forms [2].

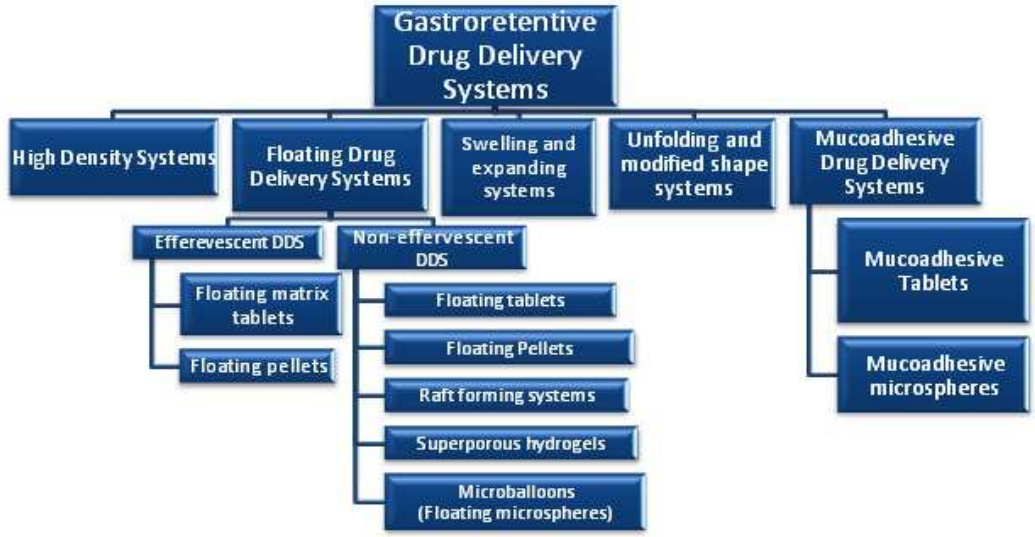

Fig. 3: Approaches for gastric retention of dosage forms

Floating systems

Floating drug delivery systems are having bulk density less than gastric fluids and therefore remain buoyant in the stomach without affecting the gastric emptying rate for extended period of time. When the system is floating on the gastric contents, the drug is released in controlled manner from the system. After release of drug, the residual system is emptied from the stomach [2].

Floating properties based on the mechanism of buoyancy are divided into:

1) Effervescent systems with low density due to gas generation and entrapment; and

2) Non effervescent systems with inherent low density or low density due to swelling.

Effervescent floating drug delivery systems

This approach provides floating drug delivery systems based on the formation of CO_2 gas. It utilizes effervescent components such as sodium bicarbonate ($NaHCO_3$) or sodium carbonate, and optionally citric or tartaric acid. Upon contact with the acidic environment, a gas is liberated, which produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chyme. Such effervescent system is often combined with swellable and rate controlling polymers like hypromellose and polyethylene oxide. Such combined system provides additional buoyancy and increased gastro retention through expanding mechanism and low density.

Zou *et al.* [8] developed a floating pulsatile drug delivery (FPRT) system of Verapamil HCl using dry coating technique. The tablet consists of bilayer tablet in which one layer is buoyant layer and other layer is composed of dry coated tablet containing drug-containing core, coated by a hydrophilic polymer which is responsible for a lag phase in the onset of pulsatile drug release. The buoyant layer, prepared with Methocel® K4M, Carbopol® 934P and sodium bicarbonate, provides buoyancy to increase the retention of the oral dosage form in the stomach. The results exhibited a certain lag time before the drug release is mainly due to the erosion of the dry coated polymer layer. Floating time was manoeuvred by the quantity and composition of the buoyant layer.

Ravi Kumar *et al.*[9] prepared floating effervescent tablets of Famotidine utilizing hydrocolloids like various grades of HPMC and Carbopol 934P and gas-forming agents like sodium bicarbonate and citric acid. The optimized formulation was subjected to various kinetic release investigations and it was found that the mechanism of drug release was predominantly diffusion with polymeric relaxation.

Someshwar *et al.*[10] prepared effervescent floating matrix tablets of Tizanidine hydrochloride using different viscosity grades of HPMC and sodium bicarbonate. Further, tablets were studied for *in vitro* drug release characteristics for 12 h. Based on the release kinetics, all formulations best fitted the Higuchi, first-order model and non-Fickian as the mechanism of drug release.

Chaitanya *et al.*[11] developed Levodopa effervescent floating tablets by direct compression method using different high molecular weight grades of Polyethylene oxide (Polyox). Among all

formulations studied, formulation containing Polyox WSR 303 in 1:1 drug polymer ratio showed controlled drug release for 12 h.

Non-effervescent floating drug delivery systems

Systems with initially low density are highly desired, since they prevent the risk of premature emptying from the stomach. Inherent low density can be provided by entrapment of air, or by the incorporation of low-density materials, such as fatty substances or oils, or foam powder. The air trapped by the swollen polymer imparts buoyancy to these dosage forms. In addition, the drug is slowly released by controlled diffusion through the gelatinous barrier.

Sheth and Tossounion developed *hydrodynamically balanced systems* (HBS™) containing homogenous mixture of gel-forming hydrocolloids and drug which upon contact with gastric fluid acquired and maintained overall specific gravity less than that of gastric contents (~1.004-1.01).[12]

Kumar *et al.*[13] has proposed glycerol monooleate (GMO) matrices as gastroretentive carrier systems. The GMO matrices were prepared by melting GMO at 55 °C on a water bath, adding the drug under stirring and pouring the molten mass into cylindrical moulds (8.5 mm inner diameter and 10 mm height) and further frozen at-15 °C. The matrices were equilibrated at room temperature for 24 h before evaluation. The GMO matrices significantly swelled in water and the swollen mass floated at the surface after a certain lag time for 5-6 h.

Yan *et al.*[14] developed *wax based floating sustained release dispersion pellets* for a weakly acidic hydrophilic drug protocatechuic acid. This low-density drug delivery system composed of octadecanol/ microcrystalline cellulose mixture matrix pellet cores prepared by extrusion-spheronization technique, coated with drug/ethyl cellulose 100cp solid dispersion using single-step fluid-bed coating method. The formulation-optimized pellets could maintain excellent floating state without lag time and sustain the drug release efficiently for 12 h based on non-Fickian transport mechanism.

Non-effervescent floating matrix tablets utilize matrices prepared using swellable and retardant polymers without any effervescent agents.

Oh *et al.*[15] developed Metformin floating gastroretentive tablets using camphor as sublimation material and PEO as hydrophilic polymer. Floating gastro-retentive tablets have no floating lag time and floated for over 24 h. The mechanism employed for drug release from the GR tablets was diffusion combined with erosion.

Negi *et al.*[16] prepared floating non-effervescent matrix tablets of Ciprofloxacin HCl using HPMC K4M and Euryale ferox seeds powder (EFSP). The floating behaviour of tablets was found to be dependent upon particle size of EFSP. Most of the formulations were best fitted with Korsmeyer-Peppas and zero order release kinetics.

Meka *et al.*[17] prepared non-effervescent floating tablets using release retarding/swellable polymers such as xanthan gum and polyethylene oxide. Formulations containing 40 mg of polyethylene oxide and 50 mg xanthan gum were found to be best, with the drug retardation upto 12 h.

Rao *et al.*[18] prepared floating matrix tablets of Ramipril using different ratio of Peanut Husk powder and HPMC K100 M. Formulation containing 6%w/w Peanut Husk Powder and 8%w/w HPMC K100M showed minimum floating lag time and>95% drug release over 12 h period.

Raft forming systems

The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. Gelation involves formation of the double helical junction zones followed by aggregation of the double helical segments which form three dimensional networks by complexation with cations and hydrogen bonding.[19] The raft floats because of the buoyancy created by the formation of CO_2 and acts as a barrier to prevent the reflux of gastric contents like HCl and enzymes into the esophagus (see fig. 4.

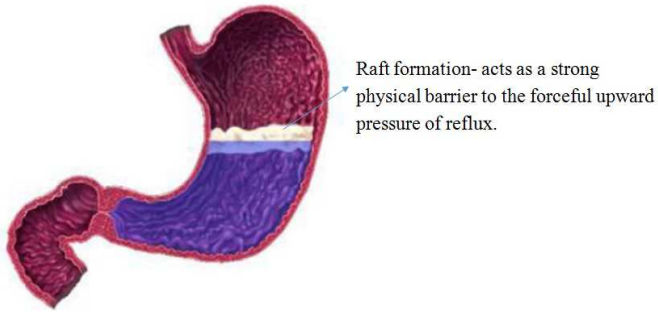

Fig. 4: Raft forming systems

Usually the system contains a gel forming agent or polymer (e. g. alginic acid), acid neutralizer and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids. Various natural and synthetic polymers can be utilized in the formulation of raft forming drug delivery systems. Natural polymers include alginic acid, guar gum, gellan gum, xyloglucan, pectin, chitosan etc. Synthetic polymers include poly (DL Lactic acid), poly (DL-lactide-co-glycolide), poly-caprolactone, HPMC etc.

Different approaches used to trigger raft formation based on their mechanisms are illustrated in following table:

Table 1: Different approaches utilized for raft based drug delivery systems[19**]**

Main approach	Type	Mechanism	Polymers utilized
Raft formation based on physical mechanism	Swelling based	Gel formation occurs when liquid effervescent system comes in contact with gastric fluid.	Swellable polymers (like HPMC) absorb water from surrounding fluid and expand at the desired space along with CO2 formation to float upon gastric fluid. Myverol 18-99 (glycerol mono-oleate), is a polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has also bioadhesive properties and can be degraded *in vivo* due to enzymatic action.
	Diffusion	Diffusion of a solvent from polymer solution into surrounding tissue, which further results in precipitation or solidification of polymer matrix.	N-methyl pyrrolidone (NMP) solution
Raft formation based on chemical mechanism	Ionic cross-linking	Various ion-sensitive polysaccharides undergo phase transition in presence of various monovalent and divalent cations and cause gelation.	• Alginic acid undergoes gelation in the presence of divalent/polyvalent cations like Ca^{2+}due to the interaction with guluronic acid block in alginate chains. • K-carrageenan forms rigid, brittle gels in response to small amount of K^{+}, i-carrageenan forms elastic gels mainly in the presence of Ca^{2+}. • Gellan gum (Gelrite®) is an anionic polysaccharide that undergoes in situ gelling in the presence of mono-and

			divalent cations, including Ca^{2+}, Mg^{2+}, $K^{+}$and Na^{+}. • Low-methoxy pectin undergoes gelation in presence of divalent cations especially Ca^{2+}.
Raft formation based on physiological stimuli mechanism	pH dependent gelling	pH sensitive polymer can be neutral or ionic in nature. In the case of anionic polymeric network containing carboxylic or sulphonic acid groups, ionization takes place, as the pH of the external swelling medium rises above the pKa of that ionisable moiety.	• Various polymers such as PAA (Carbopol®) or its derivatives, polyvinylacetaldiethylaminoacetate (AEA), mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) show change from sol to gel with change of pH. • Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. • Mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) also have been used as a pH sensitive system to achieve gelation.
	Temperature dependent gelling	These hydrogels are liquid at room temperature (20 °C–25 °C) and undergo gelation when in contact with body fluids (35 °C–37 °C), due to an increase in temperature. This approach exploits temperature-induced phase transition. Some polymers undergo abrupt changes in solubility in response to increase in environmental temperature (lower critical solution temperature, LCST). A positive temperature-sensitive hydrogel has an upper critical solution temperature (UCST), and such hydrogel contracts upon cooling below the UCST.	• Polymers such as pluronics (poly (ethylene oxide)–poly (propylene oxide)–poly(ethylene oxide) (PEO–PPO-PEO Triblock), polymer networks of poly(acrylic acid) (PAA) and polyacrylamide (PAAm) or poly(acrylamide-co-butyl methacrylate) are commonly used for temperature sensitive hydrogels formation. • Polymer networks of poly(acrylic acid) (PAA) and polyacrylamide (PAAm) or poly(acryl amide-co-butyl methacrylate) have positive temperature dependence of swelling.

The marketed preparations include Algicon® (Rorer), Liquid Gaviscon® (GSK) etc.[2]

Superporous hydrogels

Hydrogels are cross-linked hydrophilic polymers with a network structure. They are able to imbibe large amounts of water and are water insoluble.[20–22] For pharmaceutical applications, they are unique carriers for controlled drug delivery; release control can be governed by both swelling and biodegrading properties. Owing to their high water affinity and biocompatibility, hydrogels based on poly (acrylic acid) and its derivatives [23, 24], Chitosan [25], alginate [26] and collagen [27] have attracted attention.

Chen J *et al.* prepared a new generation of hydrogels called superporous hydrogels (SPH). They developed super porous hydrogels by crosslinking polymerization of various vinyl monomers in the presence of gas bubbles formed by chemical reaction of acid and sodium bicarbonate. This was followed by dehydrating water-swollen hydrogels with ethanol and drying. Equillibrium swelling time can be reduced to less than one minute.[28]

Several important properties of SPH such as fast swelling, large swelling ratio and surface slipperiness makes SPH as good candidate material for gastric retention devices.[29] Several superdisintegrants, Ac-Di-Sol®, Primojel®, Explotab®, and Polyplasdone® were used as model composite materials to promote the swelling speed and to improve the mechanical properties. Ac-Di-Sol® was found to be the best composite material among those excipients. The main role of Ac-Di-Sol® was to increase the physical crosslinking of polymer chains so that the porous structure was maintained during drying of the SPHs [29].

Superporous Hydrogel Composites (SPHCs), as the second generation of SPHs, possess improved mechanical properties over SPHs, with composite agents such as, Chitosan [30, 31] Ac-Di-Sol [32, 33] and Carbopol®[34]. After preparation of these SPHCs, they can be drilled and filled with drug-polymer mixture to provide drug delivery in sustained fashion (see 5). Alternatively, these drug filled SPHCs can also be filled in suitable size hard gelatin capsules for ease of administration.

Microballoons (Floating microspheres)

Most of the floating drug delivery systems are dominated by single unit systems. They are having cons of high variability of the GI transit time, due to its "All or nothing" emptying process. To overcome this issue, multiple unit floating systems can be designed which can be widely distributed in GI tract upon administration and provide more reliable and long-lasting drug delivery to stomach [36].

Hollow microspheres can be prepared by following techniques:

1. Solvent evaporation technique
2. Emulsion solvent diffusion technique
3. Spray drying method

These techniques are discussed in detail in following sections:

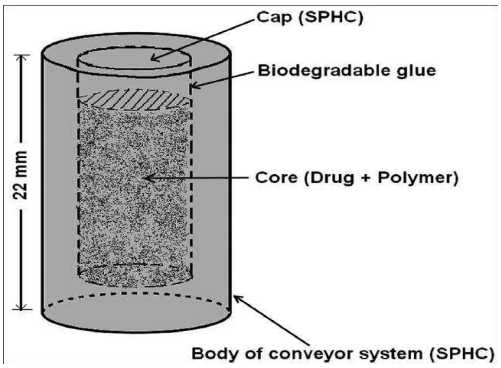

Fig. 5: Schematic diagram of SPHC-drug delivery system (Core inside the shuttle system) (Adapted from [31])

Solvent evaporation technique

There are different methods to use microencapsulation by solvent evaporation technique. The choice of the method that will give rise to an efficient drug encapsulation depends on the hydrophilicity or the hydrophobicity of drug.

For insoluble or poorly water-soluble drugs, the oil-in-water (o/w) method is frequently used. This method is the simplest and the other methods derive from this one. It consists of four major steps [37] (see 6):

(1) Dissolution of the hydrophobic drug in an organic solvent containing the polymer;

(2) Emulsification of this organic phase (dispersed phase) in an aqueous phase (continuous phase);

(3) After formation of stable emulsion, evaporation of the solvent from the dispersed phase by increasing temperature or under continuous stirring at room temperature, transforming droplets of dispersed phase into solid particles; and (4) Recovery and drying of microspheres to eliminate the residual solvent.

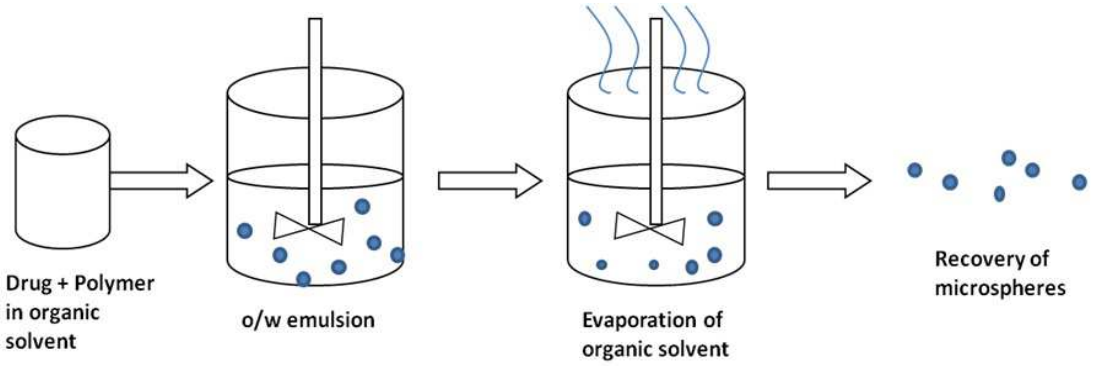

Fig. 6: Schematic presentation of microspheres preparation by solvent evaporation technique

For hydrophilic drugs, above method is not suitable due to poor solubility of drug in oil phase (dispersed phase). For such water soluble drugs following variants have been proposed by Li *et al.*[37]:

a) The w/o/w double emulsion method: the aqueous solution of drug is emulsified with organic phase (w/o emulsion) which is further dispersed into a second aqueous solution forming w/o/w double emulsion

b) The o/w co-solvent method: when the drug is not soluble in the main organic solvent, a second solvent called co-solvent is required to solubilize the drug

c) The o/w dispersion method: The drug is dispersed in form of solid powder in organic solution of the polymer

d) The o/o non-aqueous solvent evaporation method: the aqueous phase is replaced by oil such as mineral oil.

Table 2 lists the components used to prepare hollow microspheres by solvent evaporation technique

Solvent evaporation method is simplest method to form microspheres where process can be controlled easily and formed microspheres show good product yield and high encapsulation efficiency. However, this technique possesses limitation like rate of solvent removal which can affect physicochemical properties of formed hollow microspheres.

Emulsion solvent diffusion technique

Kawashima *et al.*[36] prepared hollow microspheres (microballoons) by novel emulsion solvent diffusion technique based on enteric acrylic polymers containing the drug in the polymeric shell. The preparation method and mechanism of micro balloon formation is illustrated in 7.

Table 2: List of components used to prepare hollow microspheres by solvent evaporation technique [37, 38**]**

Organic Solvents	Polymers	Surfactants
Chloroform	Ethyl Cellulose	Non-ionic: Partially hydrolyzed PVA, Tween, Span
Ethyl acetate	Hypromellose	Anionic: sodium dodecyl sulphate (SDS)
Ethyl formate	Methyl cellulose	Cationic: Cetyltrimethyl ammonium bromide (CTAB)
Dichloromethane	Cellulose acetate	
	Chitosan	
	Eudragit® RS 100	
	Eudragit® RL 100	
	Eudragit® S 100	

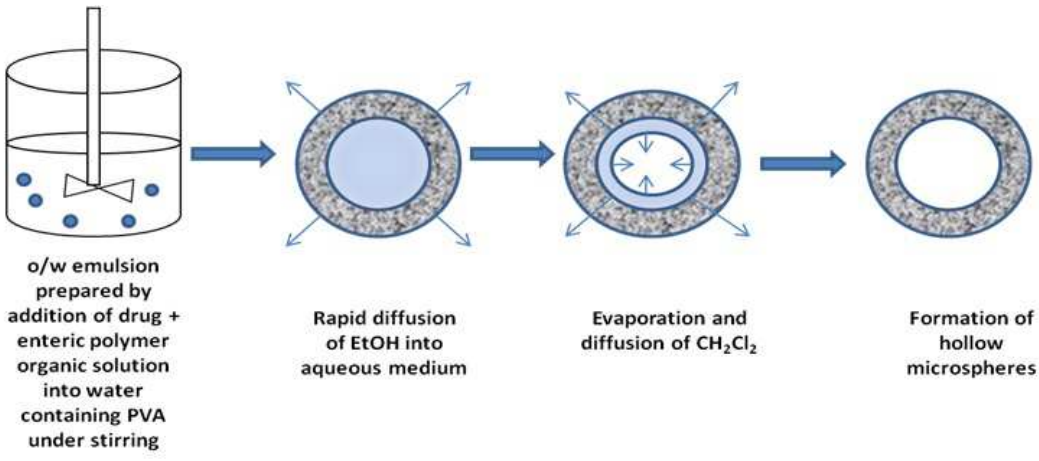

Fig. 7: Schematic presentation of microballoon preparation by emulsion solvent diffusion technique

The drug and enteric polymer were dissolved in mixture of ethanol and dichloromethane (1:1) at room temperature. The drug-polymer dispersion was poured into water containing polyvinyl alcohol at 40 °C under agitation. The ethanol rapidly diffuses into aqueous medium, and then the equilibrium concentration of ethanol was retained during the preparation of microballoons. In contrast, the dichloromethane did not diffuse thoroughly from the droplets into aqueous phase but partly resided in the droplets. During the preparation, the concentration of dichloromethane in the aqueous phase decreased due to evaporation from the system. Evaporation of dichloromethane leaves internal cavities in the microspheres which are useful for buoyancy of the microspheres. Table 3 lists the components used to prepare hollow microspheres by this technique.

Table 3: List of components used to prepare hollow microspheres by emulsion solvent diffusion technique[36, 39–43]

Organic solvents	Oil	Polymers	Surfactants	Dispersing agent	Stabilizer
Ethanol	Corn Oil	Ethyl cellulose	Span 80	Polyvinyl alcohol	Monostearin
Dichloromethane		Hypromellose	Tween 80		
Patroleum ether		Eudragit S 100			
Isopropanol		Eudragit L 100			
		Eudragit L100-55			
		Eudragit RLPO			
		Glyceryl monooleate			

Spray drying method

Spray drying is the most widely used method for particle formation and drying. It is an ideal process where the required particle size distribution is narrow and required size of products can be obtained in a single step [44]. The mechanism of spray drying can be explained as follows. First, when the slurry is sprayed into the drying chamber, concentration gradient of the solute forms inside the small droplet with the highest concentration being at the droplet surface. This ultimately results in solid shell with increase of the quantity of solutes on the surface and so the internal pressure increases because the moisture cannot be released instantly. If the shell has porous structure, the pressure can be released slowly and the hollow structure forms, otherwise fractured shell will appear. Separation of the solid products from the gases is usually achieved by means of a cyclone separator and the products are stored for further use [45].

Aute et al.[46] developed gastroretentive floating microspheres of Nizatidine using both solvent evaporation and spray drying techniques. Entrapment efficiency was found to be 60-90% for solvent evaporated microspheres, and 60-80% for spray dried microspheres. In vitro drug release for all the formulations in 0.1N HCl was diffusion controlled gradually upto 8 h and followed by first order kinetics.

Mane *et al.*[47] developed and evaluated Carvedilol microspheres by spray drying technique using ethyl cellulose and PEG 6000. The developed microspheres were in size ranging from 13-22µ and shows drug release retardation upto 12 h. However, these microspheres are having poor flowability due to cohesiveness.

Swelling and expanding systems

The expansion of this type of DDS is generally due to the presence of specific hydrogel formers, which after swallowing; drastically increase in size upon contact with aqueous media. This increase in size prevents their exit from the stomach through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be referred to as the "plug type systems" since they exhibit a tendency to remain lodged at the pyloric sphincter [7].

Unfolding and modified shape systems

These are non-disintegrating geometric shapes moulded from silastic elastomer or extruded from polyethylene blends, which extend the gastric residence time depending on size, shape and flexural modulus of the drug delivery device. Devices with different geometrical shapes such as continuous solid stick, tetrahedron, ring, cloverleaf, planer disk, string and pellet/sphere were investigated. These systems consist of at least one erodible polymer (e. g., Eudragit® E, hydroxypropyl cellulose (HPC)), one nonerodible polymer (e. g., polyamides, polyolefins, polyurethanes), and a drug dispersed within the polymer matrix. Cloverleaf, disk, string and pellet shapes were moulded from silastic elastomer, while tetrahedron and rigid-ring shapes were fabricated from blends of low-density polyethylene and ethylene: vinyl acetate copolymer [7].

Bioadhesive or mucoadhesive systems

Bioadhesive or mucoadhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface of the stomach. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, Carbopol®, lectins, chitosan, CMC etc. [49].

This type of dosage form offers following advantages:

1. Prolongs residence time in upper GIT
2. Enhances absorption and hence bioavailability of drug.
3. Improved patient compliance

Following properties are exhibited by good mucoadhesive polymers:

1. Strong hydrogen-bonding groups [-OH,-COOH]
2. Strong anionic charges
3. Sufficient flexibility to penetrate the mucus network
4. Surface tension characteristics suitable for wetting mucus/mucosal tissue surface
5. Polymer must have high molecular weight to promote adhesion between polymer and mucus.

The mucoadhesive polymers can be classified as-

a) Hydrophilic polymers: Matrices developed with these polymers swell when put into aqueous media with subsequent dissolution of the matrix. The polyelectrolytes extend greater mucoadhesive property when compared with neutral polymers. Examples are PVP, Methyl cellulose, Sodium carboxymethyl cellulose, Hydroxypropyl cellulose

b) Hydrogels: This type of polymer swells when in contact with water and adhere to the mucus membrane.

These are sub-classified as-

Synthetic polymers-Cellulose derivatives, Carbopol®

Natural polymers-Tragacanth, pectin, gelatin, sodium alginate, acacia

c) Newer second generation polymers:

i) Lectins: Lectins are naturally occurring proteins that are useful in biological recognition involving cells and proteins. Lectins are a class of structurally diverse proteins and glycoprotein that bind reversibly to specific carbohydrate residues.

ii) Thiolated polymers: These are thiomers which are derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum. The presence of thiol group increases residence time by promoting covalent bonds with the cysteine residues in mucus.

iii) Sentry Polyox WSR: These are high molecular weight polyethylene oxide having good mucoadhesion e. g. Sentry Polyox WSR 303 etc.

Mucoadhesive gastroretentive microspheres

Mucoadhesive gastroretentive microspheres are controlled drug delivery systems which provide mucoadhesion along-with gastroretention.

Mucoadhesive microspheres can be manufactured using any of the following techniques:

a) Solvent evaporation

b) Hot melt microencapsulation

c) Hydrogel microspheres

d) Spray drying

Out of above, solvent evaporation and spray drying techniques are already discussed in detail under microballoons section.

Hot melt microencapsulation

This method was first utilized by Mathiowitz and Langer [48] to prepare microspheres of poly (bis-(p-carboxyphenoxy) propane anhydride) (PCPP) copolymerized with sebacic acid (SA). Ratio of PCPP to SA was kept at 21:79. The polymer is first melted and then mixed with solid particles of the drug with particle size less than 50 µm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5 °C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers, e. g. polyanhydrides.

Hydrogel microspheres[49**]**

Microspheres made of gel type polymers, such as alginate, are produced by dissolving the polymer in an aqueous solution, suspending the drug in the mixture and extruding through a precision device, producing micro droplets which fall into a hardening bath that is slowly stirred. The hardening bath usually contains calcium chloride solution, whereby the divalent calcium ions crosslink the polymer forming gelled microspheres. The method involves an all-aqueous system and avoids residual solvents in microspheres.

Evaluation of mucoadhesion

The best approach to evaluate mucoadhesive microspheres is to evaluate the effectiveness of the mucoadhesive polymer to prolong the residence time of drug at the site of absorption, thereby increasing absorption and bioavailability of the drug. The quantification of the mucoadhesive forces between polymeric microspheres and the mucosal tissue is a useful indicator for evaluating the mucoadhesive strength of microspheres. *In vitro* techniques have been used to test the polymeric microspheres against a variety of synthetic and biological tissue samples, such as synthetic and natural mucus, frozen and freshly excised tissue, etc.

Table 4 illustrates various *in vitro* tests for evaluation of muco-adhesion of dosage forms.

Table 4: Various *In vitro* tests for mucoadhesion of dosage forms

Tests	Method
Tensile stress measurement using Wilhelmy plate technique	The Wilhelmy plate technique is generally used for the measurement of dynamic contact angles and involves the use of a microtensiometer or a microbalance. The CAHN dynamic contact angle analyzer (model DCA 322, CAHN instruments, Cerritos) has been modified to perform adhesive microforce measurements. By using the CAHN software system, three essential mucoadhesive parameters can be analyzed: fracture strength, deformation to failure and work of adhesion.
Novel electromagnetic force transducer (EMFT)	The electromagnetic force transducer (EMFT) is a remote sensing instrument that uses a calibrated electromagnet to detach a magnetic loaded polymer nanoparticle/microsphere from a tissue sample. It has the unique ability to record remotely and simultaneously the tensile force information as well as high magnification video images of mucoadhesive interactions at near physiological conditions. The EMFT measures tissue adhesive forces by monitoring the magnetic force required to exactly oppose the mucoadhesive force. The primary advantage of the EMFT is that no physical attachment is required between the force transducer and the particle.
Shear stress measurement	The shear stress measures the force that causes a mucoadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact. Adhesion tests based on the shear stress measurement involve two glass slides coated with a polymer and a film of mucus. Mucus forms a thin film between the two polymer coated slides, and the test measures the force required to separate the two surfaces.
Miscellaneous methods	Adhesion number, *in vitro* wash-off test for microspheres, falling liquid film method, everted sac technique, novel rheological approach, flow-through approach etc.

***In vitro* characterization of gastroretentive dosage forms**

There are several parameters which are commonly applicable to all types of gastroretentive drug delivery systems e. g. drug content, related substances, residual solvents etc. as per compendial or regulatory requirements. But there are specific parameters which can be adapted for evaluation depending upon type of dosage form. Various parameters need to be evaluated for gastro retention are mentioned below:

Buoyancy lag time

It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. This parameter can be measured as a part of the dissolution test.

Total floating time

Test for floatation is usually performed in SGF-Simulated Gastric fluid maintained at 37˚C. The time for which the dosage form continuously floats on the dissolution media is termed as total floating time.

Resultant weight determination

Bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time. So to measure real floating capabilities of a dosage form, novel method has been devised by Timmermans and Moes.[50] Novel apparatus (resultant weight apparatus) and method has been designed to monitor *in vitro* the total force F acting vertically on an immersed object. This force F determines the resultant weight of the object in immersed conditions and may be used to quantify its floating or non-floating capabilities. The magnitude and direction of force F, and hence resultant weight, correspond to the vectorial sum of the buoyancy (F_{buoy}) and gravity (F_{grav}) forces acting on the object.

$F= F_{buoy}-F_{grav}$

$= d_f gV - d_s gV$

$= (d_f - d_s)gV$

$= (d_f - M/V)gV$

Where F is the total vertical force (resultant weight of object); g is the acceleration of gravity; d_f the fluid density; d_s the object density; M the object mass and V the object volume.

The resultant weight apparatus operates by measuring the force equivalent to F required to maintain the object totally submerged into the fluid.[50]

Swelling index

After immersion of swelling dosage form into SGF at 37°C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness/diameter with time [51].

Water uptake

It is an indirect measurement of swelling property of swellable matrix. The study is done by immersing the dosage form in SGF at 37 °C and determining the dimensional changes like tablet diameter and/or thickness at regular intervals, the tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then reweighed and WU is measured in the terms of percent weight gain, as given by equation:

$$WU = \frac{Wt - Wo}{Wo} \times 100$$

In which Wt and Wo are the weights of the dosage form at time t and initially, respectively.

Dissolution study

Dissolution is carried out for quality control purposes and also to establish *in vitro in vivo* correlation. Traditional compendia dissolution methods have been shown to be poor predictors of *in vivo* behavior of gastro retentive dosage forms [52]. USP apparatus 2 is associated with problems like adherence of dosage form on the shaft, test does not mimic the release of acid from stomach lining and gastric emptying through pylorus opening.

In case of USP apparatus 4, the dosage form remains stationary during the test in the cell and hence floating ability cannot be examined effectively. Gohel *et al.*[52] proposed modified version of Rossett-Rice Test apparatus (see 8) which is a popular *in vitro* test for evaluating the neutralization efficiency of antacids. A 100 ml glass beaker was modified at the base by adding an S-shaped glass tube so that the glass beaker can hold 70 ml of dissolution medium. The medium was stirred on a magnetic stirrer. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min.

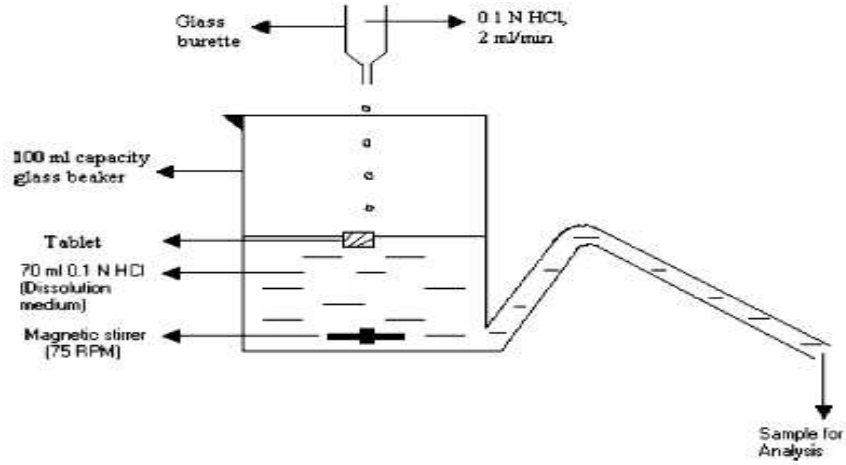

Fig. 8: Schematic presentation of the modified dissolution apparatus, (Adapted from [52])

***In vivo* characterization of gastro retentive dosage forms**

X-Ray radiography

The floating behavior of monolithic or multiple unit systems (Microballoons, minitablets etc.) can be characterized by administering the same dosage form loaded with Barium sulfate ($BaSO_4$) as radio-opaque agent, to human volunteers, beagle/mongrel dogs, albino rabbits, rats etc. the study can be conducted in fed and fasting conditions. The location of dosage form can be monitored in the gastric region at predetermined time intervals using X-Ray apparatus. Both floating time and GRT of the system can be recorded and studied [53].

Gamma (ϒ)-scintigraphy

Gamma scintigraphy is an imaging technique that enables the direct visualisation and quantification of events occurring *in vivo*, in real time. Visualisation is achieved by the incorporation of short half-life gamma emitting radionuclides, e. g. Technetium-99m (^{99m}Tc) and Indium-111 (^{111}In). The chosen radionuclide(s) is used to label the drug product or, for pharmacodynamic investigations, the component of interest (e. g. food or fluid for gastrointestinal transit). The radiation dose to the subject is minimal. A gamma camera is used to detect the gamma rays and record these as primary counts which are represented as an image. Gastric images of human volunteers or experimental animals using collimator are collected for about 1000 counts per second. The gamma scintigraphic imaging is started just after dosing and is carried out at specified time intervals under the dynamic planer conditions[53] Nowadays, combination of scintigraphy technique with pharmacokinetic studies (pharmacoscintigraphy) has become a vital tool to provide information regarding the transit and release behaviour of dosage forms with subsequent drug absorption pattern [54].

Pharmacokinetic studies

Pharmacokinetics study is performed from blood sampling estimating C_{max}, t_{max} and AUC from the observed mean drug plasma concentration against time profile. K_{el} and $t_{1/2}$ are also computed. The extent of absorption from the prepared test formulation relative to the marketed or nonfloating one is calculated as the relative bioavailability. Also, drug concentrations could be determined in urine samples at scheduled time intervals following administration. Subsequently, cumulative amount of excreted drug in urine as a function of time is measured [53].

Clinical Significance of GRDDS

Waterman *et al.*[55] has discussed regarding comparative clinical success of various types of gastroretentive dosage forms in humans. Despite the tremendous efforts have been envisaged in the field of gastroretentive drug delivery systems, only limited number of

dosage forms have succeeded to stay in stomach for extended period of time. Out of the three major GR technologies viz. mucoadhesion, floatation and expansion, only the latter appears to provide true gastric retention. To achieve adequate size to prevent passage through the pylorus yet be able to be swallowed requires very significant expansion at least in two dimensions after ingestion of dosage form. In addition, the expanded form must have adequate strength to withstand the forces in the stomach.

Potential advantages of gastroretentive drug delivery systems

Various advantages of gastroretentive drug delivery systems are outlined below[56]:

1. Improves bioavailability of P-glycoprotein substrates like Pregabalin, Gabapentin etc.

2. Increases bioavailability of drugs which are soluble at acidic pH. e. g. Dipyridamole etc.

3. Produce extended release of drugs from dosage forms

4. Can provide site specific drug delivery and therefore useful in the treatments of stomach and small intestine (e. g. for treatment of H. pylori infection)

5. Provide controlled release mode of drug administration and minimizes fluctuation in blood drug concentrations (i.e. between peak and trough). Therefore, concentration dependent side effects can be minimized.

Commercial products incorporating various gastroretention technologies

Following table summarizes some of the successful gastroretentive technologies and their commercial examples [57]

Recently granted US patents in the field of GRDDS

Following table highlights some of the recently granted US patents in the area of gastro retentive drug delivery technologies [58].

Table 5: Commercial products employing various gastroretentive drug delivery technologies

Technology	Drug	Commercial products	Company
Bioadhesive tablets	Rifaximin	Xifaxan	Lupin, India
Effervescent Floating System	Ofloxacin	Zanocin OD	Ranbaxy, India
	Metformin Hydrochloride	Riomet OD	
	Ciprofloxacin	Cifran OD	
Colloidal gel forming floating system	Ferrous Sulfate	Conviron	Ranbaxy,India
Foam based floating system	Simethicone	Inon Ace Tablets	Sato Pharma, Japan
Polymer based swelling technology: Acuform	Gabapentin	Gralise once daily	Depomed, Inc., USA
	Tapentadol	Nucynta ER	
Effervescent and swelling based floating system	Prazosin Hydrochloride	Prazopress XL	Sun Pharma
Minextab Floating System	Metformin hydrochloride	Metformin hydrochloride	Galenix, France
	Cefaclor	Cefaclor LP	
	Tramadol	Tramadol LP	
Erodible Matrix based system	Ciprofloxacin hydrochloride	Cipro XR	Bayer, USA
Expandable film filled in capsule	-	Accordion Pill	Intec Pharma
Coated multilayer floating and swelling system	Baclofen	Baclofen GRS	Sun Pharma
Gastroretentive with osmotic system	Carvedilol	Coreg CR	Glaxosmithkline
Floating CR Capsule	Levodopa and benserazide	Medopar	Roche, UK
	Diazepam	Valrelease	
Effervescent floating liquid alginate preparation	Alginic acid and sodium bicarbonate	Liquid Gaviscon	Reckitt Benckiser Healthcare, UK
Bilayer floating capsule	Misoprostol	Cytotec	Pharmacia Ltd., UK
Floating Liquid alginate	Aluminium magnesium antacid	Topalkan	Pierre Fabre Medicament, France

Table 6: List of recently granted US patents [58**]**

S. No.	US patent No	Title of patent	Publication Date/Year	Applicant/Owner
1	US 9393205 B2	Gastroretentive Tablets	19-Jul-16	Sun Pharmaceutical Industries Ltd.,Ranbaxy
2	US 9387179 B2	Pharmaceutical Cyclosporin Compositions	12-Jul-16	Sigmoid Pharma Ltd.
3	US 9381163 B2	Floating Capsules Encapsulating Particles Loaded With One Or More Drugs	5-Jul-16	Nanyang Technological University
4	US 9314430 B2	Floating Gastric Retentive Dosage Form	19-Apr-16	Jagotec Ag
5	US 9301934 B2	Gastric Retentive Dosage Forms For Extended Release Of Acamprosate Into The Upper Gastrointestinal Tract	5-Apr-16	Depomed Inc
6	US 9265722 B2	Botulinum Toxin Formulation For Oral Administration	23-Feb-16	Allergan Inc
7	US 9259387 B2	Carbidopa/levodopa Gastroretentive Drug Delivery	16-Feb-16	Intec Pharma Ltd
8	US 9211263 B2	Compositions And Methods of Treating Metabolic Disorders	15-Dec-15	Elcelyx Therapeutics Inc
9	US 9205094 B2	Compositions Comprising Bile Acid Sequestrants For Treating Esophageal Disorders	8-Dec-15	Ironwood Pharmaceuticals
10	US 9198861 B2	Methods Of Producing Stabilized Solid Dosage Pharmaceutical Compositions	1-Dec-15	Mallinckrodt Inc

		Containing Morphinans		
11	US 9192615 B2	Method For The Treatment Of Acne And Certain Dosage Forms Thereof	24-Nov-15	Medicis Pharmaceutical Corporation
12	US 9186341 B2	Gaba Conjugates And Methods Of Use Thereof	17-Nov-15	Kyphia Pharmaceuticals Inc
13	US 9161911 B2	Gastric Retentive Pharmaceutical Compositions For Treatment And Prevention Of CNS Disorders	20-Oct-15	Depomed Inc
14	US 9144559 B2	Solid Pharmaceutical Compositions Containing Pregabalin	29-Sep-15	Warner Lambert Co
15	US 9125803 B2	Gastric Release Pulse System For Drug Delivery	8-Sep-15	Shionogi Inc
16	US 9125833 B2	Multimodal Abuse Resistant And Extended Release Opioid Formulations	8-Sep-15	Relmada Therapeutics Inc
17	US 9119793 B1	Gastroretentive Dosage Forms For Doxycycline	1-Sep-15	Medicis Pharmaceutical Corporation
18	US 9060930 B2	Process For Making Gastroretentive Dosage Forms	23-Jun-15	Universite De La Mediterranee
19	US 9000046 B2	Gastric Retentive Dosage Forms For Extended Release Of Acamprosate Into The Upper Gastrointestinal Tract	7-Apr-15	Depomed Inc
20	US 8974825 B2	Pharmaceutical Compositions for Gastrointestinal Drug Delivery	10-Mar-15	Lupin Limited
21	US 8889187 B2	Once A Day Amoxicillin Product Comprising Immediate And Delayed Release Dosage Forms	18-Nov-14	Shionogi Inc.
22	US 8858963 B1	Tamper Resistant Composition Comprising Hydrocodone And Acetaminophen For Rapid Onset And Extended Duration Of Analgesia	14-Oct-14	Mallinckrodt Llc
23	US 8808669 B2	Gastroretentive, Extended Release Composition Of Therapeutic Agent	19-Aug-14	Council Of Scientific and Industrial Research
24	US 8790694 B2	Gastric Retentive Extended Release Pharmaceutical Compositions	29-Jul-14	Mallinckrodt Llc
25	US 8778396 B2	Multi-unit Gastroretentive Pharmaceutical Dosage Form Comprising Microparticles	15-Jul-14	University Of The Witwatersrand Johannesburg
26	US 8722650 B1	Extended-release Minocycline Dosage Forms	13-May-14	Medicis Pharmaceutical Corporation
27	US 8414559 B2	Gastroretentive Duodenal Pill	9-Apr-13	Rainbow Medical Ltd
28	US 8372432 B2	Gastric Retentive Extended-release Dosage Forms Comprising Combinations Of A Non-opioid Analgesic And An Opioid Analgesic	12-Feb-13	Depomed Inc
29	US 8303988 B2	Antifungal Once-a-day Product, Use And Formulation Thereof	6-Nov-12	Shionogi Inc
30	US 8277843 B2	Programmable Buoyant Delivery Technology	2-Oct-12	Panacea Biotec Limited
31	US 7947681 B2	Methods Of Administering Tetrahydrobiopterin, Associated Compositions, And Methods Of Measuring	24-May-11	Biomarin Pharmaceutical Inc
32	US 7776345 B2	Gastric Retention Controlled Drug Delivery System	17-Aug-10	Sun Pharma Advanced Res Co Ltd
33	US 6685962 B2	Gastroretentive Controlled Release Pharmaceutical Dosage Forms	3-Feb-04	Yissum Research Development Company
34	US 6207197 B1	Gastroretentive Controlled Release Microspheres For Improved Drug Delivery	27-Mar-01	Archimedes Development Limited

CONCLUSION

Present review describes recent innovations and techniques regarding fabrication and evaluation of gastro retentive drug delivery systems. Despite the numerous efforts seen in the last two decades in the field of GRDDS, only few products have been successfully reached to market due to limited clinical success for different types of GR dosage forms. Variable gastric emptying time is also one of the crucial factor for variable *in vivo* data for GR dosage forms. Gastric emptying time may largely depends upon type of food, caloric content, gender, age etc [59]. So in future, more robust GR formulations need to be designed keeping in mind various physiological barriers to get reproducible gastro-retention. Also some novel natural and modified natural polymers need to be explored in conjunction with synthetic polymers to formulate dosage forms with more swelling and expanding capabilities along-with sufficient matrix forming capabilities. This eventually results into formulation of dosage forms with better *in vivo* drug release profile with enhanced bioavailability.

This can be achieved by employing essential QbD principles and utilizing various experimental design (DOE) techniques.

CONFLICTS OF INTERESTS

Declared none

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How to cite this article

- Harshil P Shah, Shailesh T Prajapati, CN Patel. Gastroretentive drug delivery systems: from conception to commercial success. J Crit Rev 2017;4(2):10-21.